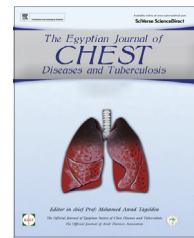




The Egyptian Society of Chest Diseases and Tuberculosis
Egyptian Journal of Chest Diseases and Tuberculosis

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ORIGINAL ARTICLE

Can brain natriuretic peptide predict the outcome in patients with acute pulmonary embolism?

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Received 15 September 2012; accepted 25 September 2012

Available online 23 January 2013

KEYWORDS

Acute pulmonary embolism;
 Brain natriuretic peptide;
 Right ventricular
 dysfunction

Abstract Risk of death is high in patients with pulmonary embolism (PE) because of right ventricular (RV) failure. Plasma levels of brain natriuretic peptide (BNP) are increased in cases of isolated chronic right ventricular dysfunction (RVD) and chronic pulmonary hypertension. However, little is known about BNP secretion during acute RVD caused by acute PE.

The aim of this study is to determine BNP levels in patients with acute PE with and without RVD and to assess its role in prediction of severity and outcome of these patients.

Patients and methods: This study was conducted on 47 patients with confirmed acute PE who were admitted to the intensive care unit (ICU) of Chest Department, Zagazig University Hospitals. Patients enrolled in this study were subjected to: (a) Transthoracic echocardiography, (b) Measurement of BNP plasma levels, (c) Measurement of D-dimer serum levels and d) Computed tomography pulmonary angiography (CTPA).

Results: There was statistically highly significant increase in plasma level of BNP (pg/mL) in patients with RVD than those without it. There were highly significant positive correlations between plasma level of BNP (pg/mL) and both RV diameter (mm) and RVSP (mmHg). A plasma BNP level > 72.5 pg/mL can predict occurrence of RVD, while a plasma level of BNP > 150 pg/mL can predict death in patients with acute PE.

Conclusion: An elevated plasma level of BNP is a prognostic factor for short-term mortality and overall short-term complicated clinical outcome, and it is a powerful indicator of RVD in patients with acute PE in the absence of left ventricular dysfunction (LVD).

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.



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Introduction

Risk of death is high in patients with PE because of RV failure. Mortality rate increases with worsening RVD. The determination of RVD is particularly important because outcome may improve with substantial afterload reduction by treatment with thrombolytic therapy [1].

Although normotensive patients with RV overload have a moderately increased in-hospital mortality rate, up to 5–13%, there is an ongoing debate as to whether this group should be treated by anticoagulation or by more aggressive methods [2].

Plasma concentrations of BNP are increased in patients with chronic heart failure and accurately predict left ventricular ejection fraction (LVEF), exercise capacity, morbidity and mortality in these patients [3].

BNP levels are also increased in cases of isolated chronic RVD and chronic pulmonary hypertension [4]. However, little is known about BNP secretion during acute RVD caused by acute PE.

The aim of this study is to determine BNP levels in patients with acute PE with and without RVD and to assess its role in prediction of severity and outcome of these patients.

Patients and methods

This study was conducted on 47 patients with confirmed acute PE who were admitted to the intensive care unit (ICU) of Chest Department, Zagazig University Hospitals between May 2010 and October 2011. They were 26 males and 21 females with a mean age of 47.3 ± 10.3 .

Inclusion criteria

Patients with acute PE were diagnosed as following [5]:

- 1- Thorough medical history taking stressing upon history of recent major surgery, prior deep venous thrombosis (DVT), cancer or pills therapy.
- 2- Typical clinical presentation: acute onset of dyspnea, tachypnea, chest pain, syncope, hypotension, and/or shock.
- 3- Laboratory: positive results of the serum D-dimer enzyme-linked immunosorbent assay (> 500 ng/mL).
- 4- CTPA.
- 5- Echocardiography: abnormal echocardiography results.
- 6- The diagnosis was further supported by lower-limbs venous ultrasound scanning examination, blood gas analysis or abnormal electrocardiogram results (tachycardia, S_I Q_{III} T_{III} type, complete or incomplete right bundle-branch block, inverted T waves in right precordial leads).

Exclusion criteria [6,7]

Patients with any of the following comorbidities which might affect natriuretic peptides levels and accuracy were excluded:

- 1- Chronic pulmonary diseases.
- 2- Chronic cardiovascular diseases.
- 3- Acute and chronic renal failure.
- 4- Endocrinal disorders as hyperaldosteronism, cushing's syndrome.
- 5- Advanced liver cirrhosis with ascites.
- 6- Anemia.
- 7- Sepsis.
- 8- Previous documented PE, prior heart failure or morbid obesity.
- 9- Severe neurological diseases as subarachnoid hemorrhage, stroke or trauma.

Patients enrolled in this study were subjected to

Transthoracic echocardiography [8]: Echocardiography was performed for all patients within the first day of admission and independent analysis was performed by a reader blinded to the clinical outcome and BNP levels of the patients. Diagnosis of RVD was made in the presence of any of these criteria:

- 1- Dilation of RV (diastolic diameter > 32 mm) or a RV/LV end-diastolic diameter ratio > 1 in the 4 chamber view.
- 2- Hypokinesis of RV.
- 3- Abnormal motion of interventricular septum.
- 4- Right ventricular systolic pressure (RVSP) > 30 mmHg, normally RVSP = 20–30 mmHg.

Measurement of BNP plasma levels. In the studied patients, blood was sampled on admission (after 6–12 h of symptoms beginning) and before initiation of therapy. B-type natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide Test (Biosite Inc., San Diego, CA). The Triage BNP Test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma [9].

The peripheral venous blood was collected (3 ml) into a sampling tube containing EDTA as the anticoagulant. Within 15 min, BNP concentrations were determined [3].

Measurement of serum D-dimer levels [10]. The levels of D-dimer were determined by an automated quantitative system, VIDAS® D-Dimer Exclusion instrument manufactured by bioMérieux® S.A. France. The assay principle combines two step enzyme immunoassay sandwich method with a final fluorescent detection, a technique called enzyme linked fluorescent assay (ELFA). Sample was collected (2 ml peripheral venous blood) in vacutainer tubes containing trisodium citrate 0.109 mol/L, (3.2%), Centrifugation at 3000 rpm for 15 min. Measurement was done following manufacturer instructions (Normal value below 500 ng/mL). The detection limits ranges from, 45 ng/mL to the upper limit of 10,000 ng/mL, samples concentration more the 10,000 ng/mL must be diluted 1/5 by special diluents in the kit and retested.

Statistical analysis

Statistical analysis was performed with the SPSS statistical software package (SPSS Inc., Chicago, IL).

Data presented by mean \pm SD for quantitative continuous data was calculated by one way analysis for variance (F test).

Qualitative data was presented by number and percentage and association was tested by Chi – square test.

P -value < 0.05 is considered significant.

Correlation coefficient (r) were calculated for testing association between quantitative variables. P -value < 0.05 is considered significant.

Receiver Operating Characteristic (ROC) curve was used for predicting cut-off levels of plasma BNP at which RVD and death occurred and area under the curve (AUC), 95% confidence interval (CI) were presented, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Kappa measurement were calculated. P -value < 0.05 is considered significant.

Results

Table 1 showed general characteristics of the studied patients. There were statistically non-significant differences between patients with and without RVD as regards age, sex, systolic blood pressure or the presence of risk factors. But, there was statistically significant increase in the presence of syncope in patients with RVD than those without RVD ($P = 0.023$).

Table 2 showed statistically highly significant increase ($P = 0.0001$) in plasma level of BNP (pg/mL) in patients with RVD than those without it, while statistically non-significant increase ($P = 0.303$) in serum level of D-dimer (ng/mL) was observed in patients with RVD than those without it. As regards PaO₂, there was statistically highly significant decrease ($P = 0.002$) in PaO₂ in patients with RVD than those without it. On the other hand, there was statistically non-significant increase ($P = 0.08$) in PaCO₂ in patients with RVD than those without it.

Table 3 showed statistically highly significant increase ($P = 0.0001$) in RV diameter (mm) and RVSP (mmHg) in patients with RVD than those without it, but there was statistically non-significant difference ($P = 0.07$) regarding LVEDD (mm). As regards RV hypokinesis, all patients with RVD had RV hypokinesis, also only 11 (47.83%) patients with RVD had abnormal motion of interventricular septum opposite non of those without RVD having these abnormalities.

Table 4 showed statistically highly significant positive correlations ($P = 0.0001$) between plasma level of BNP (pg/mL) and both RV diameter (mm) and RVSP (mmHg) in patients with RVD. While the correlation between plasma level of BNP (pg/mL) and LVEDD (mm) was statistically non-significant ($P = 0.538$) in patients with RVD.

Table 5 showed statistically highly significant negative correlations between plasma level of BNP (pg/mL) and PaO₂ both in all studied patients and in patients with RVD ($P = 0.0001$) and ($P = 0.003$) respectively.

Figs. 1 and 2 showed a receiver operating characteristic (ROC) analysis in which sensitivity was calculated with those patients who had RVD and who died during the study. The area under the ROC curve (AUC), PPV, NPV, sensitivity and specificity for cut-off levels of plasma BNP (pg/mL) were calculated in Tables 6 and 7. A plasma BNP level > 72.5 pg/mL had high sensitivity (95.7%) in predicting RVD in patients with acute PE with normal left ventricular (LV) systolic function. Also, at this cut-off level, the PPV and NPV for detection of RVD were 73.3% and 94.1% respectively with low specificity which was 66.7% ($P = 0.0001$). A plasma level of BNP > 150 pg/mL had sensitivity of 80%, specificity of 78.6%, PPV of 30.8% and high NPV of 97.1% in predicting mortality in patients with acute PE ($P = 0.006$).

Table 8 showed the outcome of the studied patients during hospitalization and there was statistically significant increase ($P = 0.041$) in the duration of hospital stay in patients with RVD than those without it. Shock, resuscitation, the need for MV and in-hospital death occurred only in patients with RVD.

Discussion

The diagnosis of RVD in acute PE is of utmost importance, because RVD is associated with mortality and there is evidence that clinical outcome can be improved by rapid dissolution of the thrombi with thrombolytic therapy [11]. Echocardiography is a readily available and generally accepted sensitive bedside method for detection of RVD [8]. However, the possibility of

Table 1 General characteristics of the studied patients with and without RVD.

Characteristic	With RVD ($n = 23$)	Without RVD ($n = 24$)	<i>P</i> -value
Age (years)	46.96 \pm 7.8	47.75 \pm 10.08	0.765
Sex, no (%):			
Male	14 (53.8%)	12 (46.2%)	0.454
Female	9 (42.9%)	12 (57.1%)	
Symptoms, no (%):			
Dyspnea	18 (51.4%)	17 (48.6%)	0.55
Chest pain	13 (48.1%)	14 (51.9%)	0.9
Syncope	7 (87.5%)	1 (12.5%)	0.023
Systolic blood pressure (M \pm SD)	112.39 \pm 10.36	114.17 \pm 8.81	0.627
Risk factors, no (%):			
Recent major surgery	7 (70%)	3 (30%)	0.168
Prior DVT	6 (60%)	4 (40%)	0.43
Cancer	1 (16.7%)	5 (83.3%)	0.188
Pills therapy	1 (25%)	3 (75%)	0.6

Table 2 Laboratory findings of the studied patients with and without RVD.

Parameter	With RVD ($n = 23$)	Without RVD ($n = 24$)	<i>P</i> -value
Plasma BNP (pg/mL)	170 \pm 85.84	67.13 \pm 9.58	0.0001
Serum D-dimer (ng/mL)	2179.38 \pm 929.6	1936.09 \pm 638.32	0.303
PaO ₂ (mmHg)	66.48 \pm 12.66	77.92 \pm 10.81	0.002
PaCO ₂ (mmHg)	39.87 \pm 15.69	33.46 \pm 7.63	0.08

Table 3 Comparison between the studied patients with and without RVD as regards echocardiographic findings.

Parameter	With RVD (<i>n</i> = 23)	Without RVD (<i>n</i> = 24)	<i>P</i> -value
LVEDD (mm)	40.83 ± 6.32	37.29 ± 7.1	0.07
RV diameter (mm)	39.09 ± 9.12	25.17 ± 3.38	0.0001
RV hypokinesis, no (%)	23 (100%)	0.0	–
Abnormal motion of interventricular septum, no (%)	11 (47.83%)	0.0	–
RVSP (mmHg)	34.52 ± 9.44	24.71 ± 2.33	0.0001

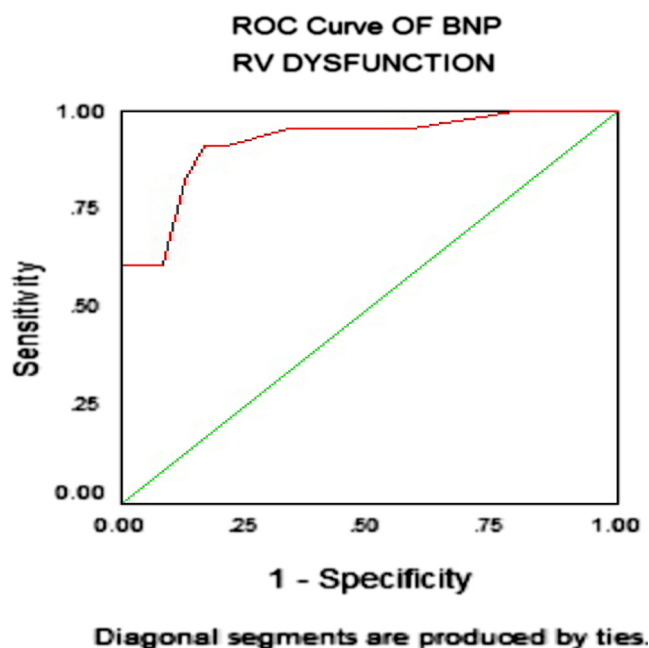
Table 4 Correlation between plasma level of BNP (pg/mL) and echocardiographic findings in patients with RVD.

Plasma BNP (pg/mL)	LVEDD (mm)	RV diameter (mm)	RVSP (mmHg)
<i>r</i> -value	0.092	0.796	0.611
<i>P</i> -value	0.538	0.0001	0.0001

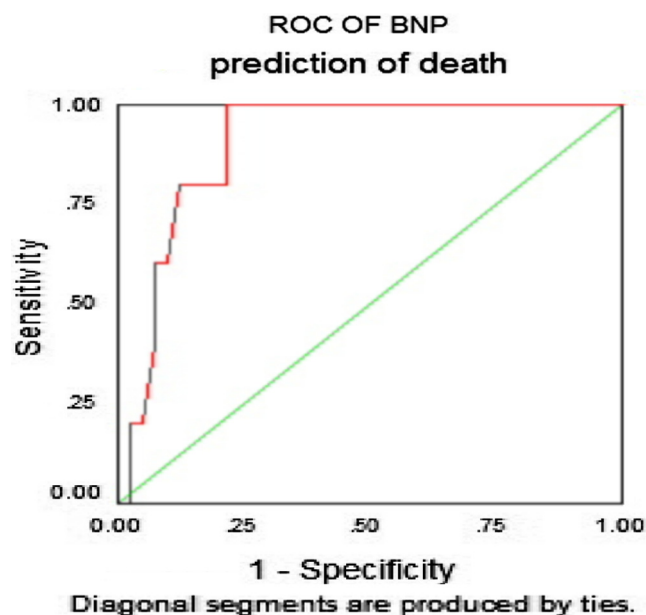
Table 5 Correlation between plasma level of BNP (pg/mL) and both partial arterial oxygen tension (PaO₂) and partial arterial carbon dioxide tension (PaCO₂) in all studied patients and in those with RVD.

Plasma BNP (pg/mL)	All studied patients	Patients with RVD
PaO ₂ (mmHg)	−0.611**	−0.583**
PaCO ₂ (mmHg)	0.277	0.147

** *P* < 0.01.

**Figure 1** ROC curve for prediction of RVD in acute PE.

implementing a rapid and effective triage with biohumoral markers such as BNP may be of value [12]. The availability

**Figure 2** ROC curve for prediction of death in acute PE.**Table 6** Prediction of both RVD and mortality for all studied patients: area under the receiver operating characteristic (ROC) curve plot analysis.

	Cut-off level	AUC	95% CI
RVD	> 72.5	0.923	0.846–1.000
Death	> 150	0.90	0.81–0.99

Table 7 Sensitivity, specificity, PPV and NPV at cut-off levels of both RVD and mortality of plasma BNP (pg/mL).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa	<i>P</i> -value
RVD	95.7	66.7	73.3	94.1	0.62	0.0001
Death	80	78.6	30.8	97.1	0.34	0.006

of biomarkers like BNP or NT-proBNP able to identify RVD patients early and to contribute to risk stratification is potentially important, especially when echocardiography assessment is not available [13].

Table 8 Outcome of the studied patients with and without RVD.

Parameter	With RVD (<i>n</i> = 23)	Without RVD (<i>n</i> = 24)	<i>P</i> -value
Shock, no (%)	6 (100%)	0.0	–
Resuscitation, no (%)	4 (100%)	0.0	–
Need for M.V., no (%)	7 (100%)	0.0	–
Duration of hospital stay (<i>M</i> ± <i>SD</i>)	20.25 ± 2.36	18.17 ± 4.18	0.041
In-hospital death, no (%)	5 (100%)	0.0	–

M.V.: mechanical ventilation.

In contrast with echocardiography, biochemical markers can be promptly obtained in all patients with acute PE and could be more suitable in this setting. A biomarker-based stratification is relevant mainly in hemodynamically stable patients whose adverse outcome cannot be easily predicted by clinical examination [14]. So, the aim of this work is to determine plasma level of BNP in patients with acute PE with and without RVD and to assess its role in prediction of severity and outcome of these patients.

BNP is produced to a larger degree from ventricular myocytes. The principal stimulus for BNP synthesis and secretion is cardiomyocyte stretch [15].

Elevated plasma levels of BNP have been found in patients with congestive heart failure and even in those with asymptomatic LV systolic dysfunction. Moreover, elevated plasma BNP was found in patients with primary pulmonary hypertension and chronic thromboembolic pulmonary hypertension [16]. Interestingly, elevated plasma BNP was reported to help differentiate pulmonary from cardiac aetiologies of acute dyspnea [17].

In our study, there was statistically highly significant increase in plasma level of BNP (pg/mL) in patients with RVD than those without it, while statistically non-significant increase in serum D-dimer level (ng/mL) in patients with RVD than those without it was observed (Table 2). Regarding echocardiographic findings in our study, there was statistically highly significant increase in RV diameter (mm) and RVSP (mmHg) in patients with RVD than in those without it. But, there was statistically non-significant difference between patients with and without RVD as regards LVEDD (mm). RV hypokinesis was observed only in patients with RVD and 11 (47.83%) patients with RVD had abnormal motion of interventricular septum (Table 3). Also, in our study, there were highly significant positive correlations between plasma level of BNP (pg/mL) and both RV diameter (mm) and RVSP (mmHg) (Table 4).

Plasma BNP elevation in acute PE is probably caused by increased myocardial shear stress, mainly in the right ventricle, and depends on the degree and dynamics of embolic events [18].

Prohormone in normal ventricular myocytes is not stored to a significant amount. Thus, it takes several hours for the plasma natriuretic peptides levels to increase after the onset of acute cardiomyocyte stretch. This includes myocardial BNP messenger ribonucleic acid (mRNA) synthesis, prohormone synthesis and plasma release [19].

In consistence with our results, Pruszczyk et al. [20] reported that plasma NT-proBNP was increased in almost all cases of clinically massive and submassive acute PE, which

are accompanied by RV overload and dyspnea, while in patients without echocardiographic signs of RVD, NT-proBNP elevation was found in only 50% of patients.

Also, Kruger et al. [8] noticed elevated BNP levels in 64% of their patients with RVD, but in only 6% of the patients without dysfunction.

Supporting our results, Kruger et al. [21] found highly dynamic BNP release kinetics with rapidly falling BNP levels after initiation of therapy, especially after thrombolysis.

Regarding echocardiography results, a sudden increase in pressure load on the RV is poorly tolerated due to the inability of its thin wall to develop and sustain high wall tension and stress. The increase in right ventricular pressures may result in shifting of the interventricular septum toward LV, reducing the left ventricular volume [22]. Myocardial wall stress is a potent stimulus for the increased synthesis and secretion of BNP, which gives the biological plausibility for elevation of BNP and NT-proBNP in the setting of acute PE and RV strain [23].

In agreement with our results, Klok et al. [24] demonstrated very strong correlation between increased levels of BNP and RVD on echocardiography in patients with acute PE. Also, Tulevski et al. [25] reported that in isolated chronic RV overload, BNP levels are elevated and correlate positively with mean pulmonary artery pressure and RV end-diastolic pressure and negatively with cardiac output and RV ejection fraction.

Regarding D-dimer results, D-dimer levels could be related to the extent of thrombotic load [26]. The association between D-dimer levels and the presence of RVD at CT angiography was evaluated in previous studies. Ghanima et al. [27] and Gutte et al. [28] reported that a positive correlation was found between RVD at CT angiography and D-dimer levels, while in Jeebun et al. [29] and Turedi et al. [30] studies, this correlation was not confirmed. A positive association was found in one study between D-dimer levels and RVD at echocardiography [31].

D-dimer appears to be a relatively poor predictor of prognosis in PE in multi-variable analysis [32].

Biochemical markers of myocardial stretch (e.g. BNP) may be more sensitive in the detection of RV overload than echocardiography [20] and biomarker determination in stable acute PE patients appears to be a valuable diagnostic adjunct, and in some cases may even substitute echocardiography in in-hospital and long-term risk stratification [33]. This is because; echocardiography suffers from several limitations as; it is a user-dependent method, not fully reproducible and it is not always immediately available [34]. Also, a number of echocardiographic parameters have been proposed to analyze RVD. Some of them are difficult to obtain and/or are missing [14].

In some studies, RV echocardiographic analysis was insufficient in more than 10% of patients which could explain discrepancies regarding RVD – related prognosis among studies.

Regarding hypoxemia in this study, there was statistically highly significant decrease in PaO_2 in patients with RVD than those without it (Table 2). Also, there were statistically highly significant negative correlations between plasma level of BNP (pg/mL) and PaO_2 both in all studied patients and in patients with RVD (Table 5).

In consistence with our results, Goldhaber and Elliott [5] reported that a low pressure of oxygen in venous blood may contribute to arterial hypoxemia when PE causes RV failure. Also, Pruszczyk et al. [20] found that increased plasma NT-proBNP and decreased oxygen saturation influenced in-hospital deaths and serious adverse events.

To evaluate the potential to predict the occurrence of RVD and also death from acute PE in clinically stable patients, a receiver operating characteristic (ROC) analysis was performed (Figs. 1 and 2). A plasma BNP level >72.5 pg/mL had high sensitivity (95.7%) in predicting RVD in patients with acute PE with normal LV systolic function. Also, at this cut-off level, the PPV and NPV for detection of RVD were 73.3% and 94.1% respectively with low specificity which was 66.7% (Table 7). But, a plasma level of BNP >150 pg/mL had sensitivity of 80%, specificity of 78.6%, PPV of 30.8% and high NPV of 97.1% in predicting mortality in hemodynamically stable patients with acute PE (Table 7).

Our results are in consistence with Kruger et al. [8] who reported that a BNP level of 75 pg/mL was a cut-off value in their study for ruling out RVD, which is close to our result.

Mikulewicz and Lewczuk [33] demonstrated that the cut-off value to diagnose 95% of patients with mild disease course was <50 pg/mL. But, Pieralli et al. [35] reported a BNP level of <85 pg/mL was shown to exclude echocardiographic findings of RV overload in normotensive patients with acute PE with a high degree of accuracy and this result is consistent with our result.

Regarding mortality prediction, Cavallazzi et al. [23] found that patients with acute PE who showed in-hospital mortality had an elevated BNP level utilizing a cut-off level of 100 pg/mL and this level is in accordance with this study. In contrast, Mikulewicz and Lewczuk [33] reported that all patients with acute PE with BNP over 527 pg/mL revealed RV overload features in echocardiography; all acute complications and deaths occurred in these patients.

Regarding the severity of acute PE and its outcome during hospitalization of our studied patients, there was statistically significant increase in the number of patients who had syncope [7(87.5%)] and in the duration of hospital stay in patients with RVD than those patients without it (Tables 1 and 8). But, there was statistically non-significant difference in systolic blood pressure between patients with and without RVD (Table 1). Also, we found shock, resuscitation, the need for M.V. and in-hospital death only among patients with RVD and with elevated BNP (Table 8).

The hemodynamic response to PE depends on the size of the embolus, coexistent cardiopulmonary disease and neuro-humoral effects [5].

Normotensive patients with acute PE and no evidence of RVD generally have a benign hospital course, while patients

with RVD on echocardiography have an increased risk of hypotension, cardiogenic shock and early death [36].

No reliable clinical parameter could differentiate patients with RVD from the others. This subgroup of patients with silent RVD, so-called sub-massive PE, has a high risk of death or hemodynamic instability during the first days of admission [37]. Logeart et al. [14] observed a high proportion of patients with acute PE with echocardiographic evidence of RVD with neither hypotension nor evidence of heart failure.

Previous studies or surveys reported that in-hospital prognosis of patients with RVD was worse than that of patients without RVD. Consequently, aggressive treatment such as thrombolysis has been proposed in these patients [38].

Supporting our results, Pieralli et al. [35] and Tulevski et al. [39] reported that 29% of their normotensive patients with acute PE had increased BNP at presentation and this high level of BNP predicted early complications. Also, Klok et al. [24] meta-analysis demonstrated a significant relation between high levels of BNP and deterioration of clinical condition in patients with acute PE.

Also, Lippi and Targher [40] and Jimenez et al. [41] reported that in hemodynamically stable patients with acute PE, there is a significant association between PE-specific mortality and raised natriuretic peptides and the NT-proBNP levels might provide faster and equally reliable prognostic information as that provided by echocardiography alone.

In contrast, Kruger et al. [21] demonstrated that all patients with acute PE presenting with syncope necessitating cardiopulmonary resuscitation showed normal BNP levels. Thus, normal BNP levels don't exclude severe PE. This might be due to an insufficient time span for RV BNP production and secretion as a consequence of sudden RV pressure overload resulting in syncope with cardiac arrest in those patients and this is the most serious obstacle against BNP use in PE patients.

Also, Coutance et al. [13] found that BNP levels may not correlate well with cardiovascular outcomes in some patients with PE of acute onset because of the obligatory delay in BNP mRNA upregulation and subsequent protein release in the serum. Indeed, it takes several hours for the BNP levels to increase after the onset of acute myocardial stretch.

Markers of RVD (i.e. echocardiography, spiral CT or BNP testing) and myocardial injury (i.e. cardiac troponin T or I testing) identify high risk normotensive patients with PE. So far, a single test has not had a sufficient positive predictive value for PE - specific mortality to guide the initiation of thrombolytic therapy. Future studies should assess if the combination of complete lower limb compression ultrasound (CCUS) testing with prognostic tools indicating myocardial injury or RVD might offer an advantage compared with each test alone with regard to the identification of normotensive patients with acute PE at high-risk of PE-associated mortality [41].

Conclusion

An elevated plasma level of BNP is a prognostic factor for short-term mortality and overall short-term complicated clinical outcome, and it is a powerful indicator of RVD in patients with acute PE in the absence of LVD.

While plasma BNP measurements may become part of the risk stratification in acute PE, its positive predictive value alone remains low and its high negative predictive value is certainly more useful to identify patients with RVD (at cut-off level > 72.5 pg/mL) and also to predict mortality of patients (at cut-off level > 150 pg/mL).

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